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Oral Malignant Melanoma

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1. Introduction

It is generally accepted that the outcome of oral malignant melanoma is worse than that of cutaneous and systemic head and neck melanoma. The five-year survival reported in the literature for oral melanomas varies from 0 - 20 % (Liversedge, 1975, Rapidis et al., 2003, Rapini et al., 1985), whereas the overall survival for head and neck melanomas ranges between 20 and 48 % (Guzzo et al., 1993, Patel et al., 2002, Stern and Guillamondegui, 1991, Temam et al., 2005), confirming anatomical site specific variation.

Treatment modalities for primary oral melanoma include surgical resection with or without neck dissection. Adjunctive modalities such as immunotherapy, chemotherapy and radiation therapy may offer a supportive but as yet non curative role. The mainstay of curative treatment is surgery, mandating complete resection of the tumor with clear margins if possible (Rapini et al., 1985, Umeda and Shimada, 1994). Immunotherapy and chemotherapy are techniques which are the subject of controlled trials or palliation (Mendenhall et al., 2005). The rarity of oral malignant melanomas means that to date no randomized clinical trials have been conducted to establish an evidence base in the literature to provide comparisons of treatment modalities. The efficacy of surgery with planned supplementary radiotherapy remain unresolved and continue to generate controversy (Patel et al., 2002).

Due the rarity of this disease, there is a lack of consistency in immunohistochemical confirmation of the diagnosis, staging strategies and treatment planning as diagnostic techniques and treatment have evolved over recent years in melanoma is other body sites and attempts have been made to translate these to the much rarer oral melanoma. This book section would like to aid the reader in understanding the current state of etiology, epidemiology, and treatment modalities of this very rare but aggressive tumor entity.

2. Oral malignant melanoma

The diagnosis of oral malignant melanoma often remains difficult. Differential diagnoses should include benign as well as malignant lesions and exogenous pigmentations can be often found (Figure 1). It also needs to be borne in mind that amelanotic malignant melanoma can affect the mouth, comprising one third of all oral malignant melanomas.

Fig. 1. Oral pigmentation due to inoculation of amalgam after dental treatment in the left buccal mucosa.

The histological spectrum of benign pigmentations is wide: macular hyperpigmentation caused by junctional proliferation with or without cellular atypica, melanocytic naevi (Figure 2), such as junctional, compound, subepithelial, blue and combined naevi. Other causes of oral pigmentation include: race, Peutz-Jeghers syndrome (Daley and Armstrong, 2007), Laugier-Hunziker syndrome (Mowad et al., 1997), Addison´s disease (Lamey et al., 1985), patients with pulmonary diseases, especially in lung cancer (Merchant et al., 1976), and hemosiderosis.

Fig. 2. Melanocytic naevi in the upper left vestibule.

Some authors describe a preexisting oral pigmentation for several month or years in one third of all patients with a primary oral malignant melanoma (Chaudhry et al., 1958, Liversedge, 1975, Rapini et al., 1985), although others found no correlation (Meleti et al., 2007). The appearances of oral malignant melanomas vary and should always be considered in oral lesions without the tendency to heal (Figure 3). Remember that about 1/3 of all oral malignant melanomas are not pigmented (Anneroth et al., 1973, Chaudhry et al., 1958, Greene et al., 1953, Lengyel et al., 2003, Liversedge, 1975, Rapidis et al., 2003).

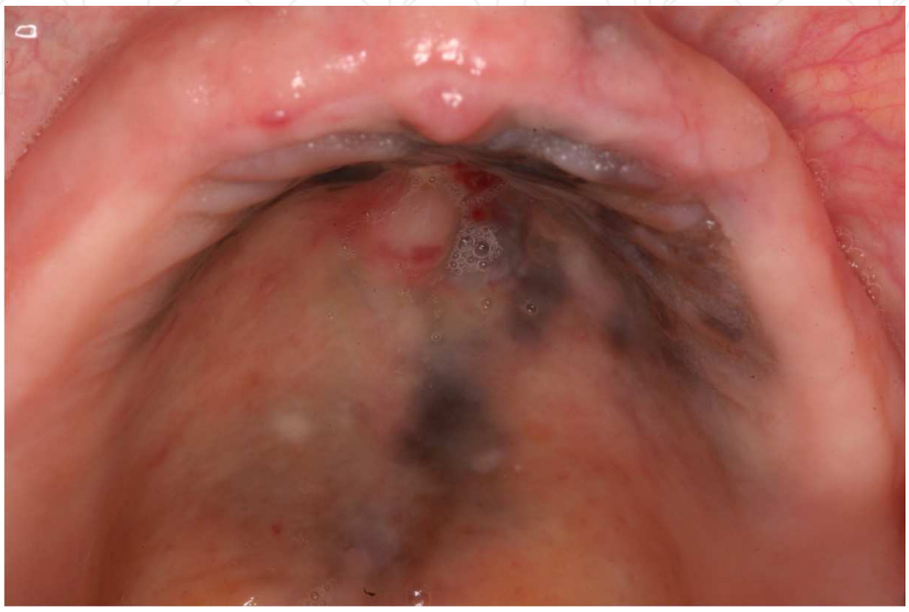

Fig. 3. Intraoral view of a malignant melanoma arising from the palate.

2.1 Etiology

Melanomas are categorized into four different types according to anatomic region and pathological factors: 1. melanomas arising from skin without chronic sun damage, 2. melanomas on skin with chronic sun damage, 3. acral melanomas, and 4. mucosal melanomas (Curtin et al., 2006). The etiology of primary oral malignant melanoma is still unknown. Cigarette smoking, denture irritation and alcohol have been mentioned as possible risk factors, but evidence remains obscure. Intraoral malignant melanomas arise from melanocytic cells of the oral cavity, which represent a minority of all cells of the mucosal membrane. Although just a few melanocytes are present in the oral mucosa the potential to develop malignant melanomas clearly exist. Indeed it is recognized that malignant melanoma can very rarely develop in almost any organ suggesting that circulating melanocytes may be responsible. About 5-30 % of primary malignant melanomas are preceded by oral pigmentations for months or even years. It has been suggested that melanosis represents the initial phase characterized as the radial phase of growth and precedes the invasion of underlying tissues (vertical growth) by years, however the histological spectrum of benign pigmented lesions is wide and a pre-existing pigmented lesion is not usually associated with mucosal melanomas. Most arise as new lesions, from apparently healthy mucosa.

Malignant melanomas develop from melanocytes derived from the neural crest. The most frequently primary sites in the oral cavity are the palate and maxillary gingiva (Barker et al., 1997, Hicks and Flaitz, 2000, Lee et al., 1994). Mucosal melanomas are considered to be more aggressive tumors compared with cutaneous melanomas and they are more inclined to metastasize into regional and distant sites, recur locally or regionally resulting in a high rate of disease specific-death.

2.2 Epidemiology

Malignant melanoma in the head and neck area is rare. Oral cavity primary malignant melanoma comprises 6.3 % of all melanomas in the head and neck area and only about 0.7 – 1.6 % of all melanomas arise in the oral mucosa (Chang et al., 1998, Moore and Martin, 1955). The incidence of primary mucosal melanomas of the head and neck is approximately four per 10 million population per year (Hicks and Flaitz, 2000). The most frequently affected oral sites are the palate and maxillary gingiva (Barker et al., 1997, Hicks and Flaitz, 2000, Lee et al., 1994). The incidence in Japan is much higher than in western countries, in which it occurs with less than 1% (Batsakis, 1982, Brandwein et al., 1997, Umeda and Shimada, 1994). The age of the patients varies between 20 and 80 years, the mean age reported in the literature ranges from 56 to 66.5 years (Gorsky and Epstein, 1998, Hicks and Flaitz, 2000, Patel et al., 2002, Rapidis et al., 2003, Rapini et al., 1985) and a modest male preponderance has been described (Rapini et al., 1985).

2.3 Prognosis

The prognosis is adverse. Due to delayed diagnosis early invasion of surrounding tissue, local lymph node involvement and distant metastasis, the prognosis of oral mucosal melanomas is very poor. The reported 5-year survival rates vary in the literature between 6 and 18 % but also between 45 and 48 % (Enroth CM, 1975, Lee et al., 1994, Lund, 1993, Ravid and Esteves, 1960, Stern and Guillamondegui, 1991). Gingival melanoma has a slightly better 5-year survival rate (18%) than that of palatal melanoma (11%), with a longer median survival period (46 months vs. 22 months). These wide variations are probably due to the fact that comparable classifications are still not agreed internationally. The routine use of tumor thicknessof mucosal melanomas, as described by the Breslow or the Clark levels are not widely performed as a routine method in everyday experience (Prasad et al., 2003, Prasad et al., 2002, Thompson et al., 2003). Therefore an evidence base derived fromhistopathological assessment and subsequent prognosis for malignant mucosal melanomas is lacking.Despite this many reports show a correlation between tumor thickness and prognosis (Mücke et al., 2009, Prasad et al., 2004). Many authors agreed that the survival rate was not only closely related to the stage of the tumor, but the treatment that patients received (Mücke et al., 2009, Prasad et al., 2003, Prasad et al., 2004, Rapidis et al., 2003, Rapini et al., 1985, Tanaka et al., 2004, Temam et al., 2005).

The vast majority of the head and neck mucosal melanomas are Stage 1 at the time of presentation , Prasad et al defined a 3-level-microstaging system, which represents different microanatomical compartments separated by tissue barriers. They found out that this microstaging system is prognostically significant and an independent predictor concerning the 5-year survival rate and the recurrence-free survival (Mücke et al., 2009, Prasad et al., 2004). In 2009, the American Joint Committee on Cancer (AJCC) Melanoma Staging Committee used previously published guidelines and determined criteria which were used

in the TNM classification and the stage groupings (Balch et al., 2009). These criteria are established for all kinds of melanomas and are proposed as follows:

1. In patients with localized melanoma, tumor thickness, mitotic rate, tumor burden, and ulceration were the most important prognostic factors.
2. The mitotic rate indicates the level of invasion as a primary criterion for defining T1b melanomas.
3. Components that defined the N category were the presence and number of metastatic nodes of the primary melanoma.
4. All patients with microscopic nodal metastases, regardless of extent of tumor burden, are classified as stage III.
5. On the basis of a multivariate analysis of patients with distant metastases, the two dominant components in defining the M category continue to be the site of distant metastases and an elevated serum lactate dehydrogenase level.

Factors that have been associated with worse disease-specific survival include clinical stage at presentation, thickness of the tumor, tumor burden at the time of staging (microscopic vs. macroscopic), presence or absence of primary tumor ulceration, presence of vascular invasion, melanosis, and development of nodal and distant metastasis ($p < 0.001$) (Balch et al., 2009). Multiple local recurrences are the most common cause of treatment failure and may occur 10-15 years after primary treatment. The most common sites of distant metastases include the lungs, brain, liver and bones.

2.4 Staging

The criteria to verify the presence of a primary intraoral melanoma are:

1. demonstration of clinical and microscopic tumor in the oral mucosa
2. presence of junctional activity in the lesion
3. inability to show any other primary site.

All patients have to fulfill all these criteria to verify the diagnosis of primary oral malignant melanoma (Greene et al., 1953). In addition to the standard staging procedure, patients should be observed by means of: sonography, gastroscopy and bronchoscopy in order to exclude other potential primary sites and confirm by exclusion the diagnosis of primary oral mucosal malignant melanoma (Mücke et al., 2009). It is important to confirm the comparatively rare finding of primary oral mucosal malignant melanoma is supported by exclusion of other potential mucosal sites for example the respiratory and the gastrointestinal tract, which are more frequently found than oral melanomas (Lee et al., 1994, Mendenhall et al., 2005, Prasad et al., 2003).

Patients should be staged according the TNM Melanoma Staging System of the American Joint Committee on Cancer which includes in the staging the extent of the tumor status as well as the extent of the nodal status, but does not provide a specific guideline for oral mucosal melanomas. Therefore a simplified staging system has been established, which classifies tumors in 3 stages: Stage I to localized disease, confined to the primary site, stage II the primary lesion with cervical lymph node metastasis and stage III for distant metastasis.

As previously described there is a 3-level-microstaging system which relates to the prognostic outcome. In this system each level represents a microanatomical compartment, which is defined through tissue barriers.Breach of each barrier correlates with a progressively worse survival rate. Level I is defined as an in situ mucosal melanoma or microinvasion, Level II as an invasion limited to lamina propria and Level III is defined as melanoma with a deep invasion into surrounding tissue such as bone cartilage or skeletal muscles.

2.5 Histopathology

The surface architecture from oral melanomas ranges from macular to ulcerated and nodular. As recommended at the WESTOP (Western Society of Teachers of Oral Pathology) Banff Workshop, oral malignant melanomas should be separately considered from the cutaneous forms and proposed to subclassify them according to the histological pattern into: in situ melanoma, invasive, combined (invasive melanoma with in situ components) and atypical melanocytic proliferation (in case where diagnosis is equivocal) (Barker et al., 1997). In situ melanomas are limited to the epithelium and the epithelial-connective tissue interface, and represent 15% of the oral melanomas. They show a proliferation of atypical melanocytes characterized through hyperchromatic and angular nuclei with infrequent mitotic activity. The melanocytes may be arranged irregularly at the epithel connective tissue-interface or may be distributed in aggregates.

Invasive pattern in which the melanoma extend into the connective tissue is represented in 30% of oral melanoma, showing a wide range of cell types including spindle, plasmocytoid, clear cells and epithelioid, arranged into sheets or organoid/alveolar formation. The large and vesicular nuclei appear frequently with prominent nucleoli and rare mitosis. 55% of oral melanomas having combined pattern, which is typical for advanced lesions (Barker *et al.* 1997, Femiano *et al.* 2008).

In most instances melanomas contain melanin pigmented tumor cells but amelanotic melanoma show a lack of melanin production, which exacerbates the correct diagnosis, because amelanotic melanoma can mimic a variety of poorly differentiated carcinoma or cell lymphoma. For distinguishing these melanomas from other tumors immunohistochemical stains have been proven to be helpful**.** For differential diagnosis, it should be claimed that immunhistochemical staining of the following markers is mandatory and the basis of the diagnosis of an oral malignant melanoma.

Immunohistochemical markers include S-100 protein, gp100 (HMB-45) and Mart-1 (Melan-A) (Messina et al., 1999). These markers are also used for the identification of micrometastases in lymph nodes (Messina et al., 1999).

The Antibody HMB-45 reacts with the melanosomal glycoprotein gp100, showing a positive staining in active early melanosome formation and showing epithelioid lesions intensily immunoreactive for HMB-45. It is considered as more specific but less sensitive than the S-100 protein, an acidic calcium binding protein, which is a very sensitive marker for nevus and melanoma cells, and even spindled lesions appear intensely immunoreactive for S-100 protein (Blessing et al., 1998, Gazit and Daniels, 1994). Melan-A is considered to be specific for melanoma cell lines, as a product of the MART-1 gene it is a melanocytic differentiation marker which is recognized on melanomas as an antigenic target of T lymphocytes (Kawakami et al., 1994).

In recent years some molecular markers, like the Ki67 antigen emerged as potentially prognostical indicators, however the role of potential therapeutic relevance of KIT inhibitors in mucosal melanoma further needs to be investigated.

2.6 Therapy

Regarding the treatment of the four types of melanomas, melanomas arising from skin without chronic sun damage, melanomas on skin with chronic sun damage, acral melanomas and mucosal melanomas, most authors agree that radical ablative surgery with wide local excision of the primary lesion and dissection of metastatic lymph nodes are the basis of every curative therapy (Curtin et al., 2006). Controversial points are the margin of

the excision, the optimal time to dissect the local lymph nodes, and the uncertainty of the extent of lymph nodes dissection. Surgery is the mainstay of treatment but can only be accomplished if vital parts of the body are not affected and therefore anatomical limitations often make a radical excision impossible.
The following protocol refers to the extent of margins:

1. Excision of the primary lesion including at least 1 – 2 cm of healthy tissue based on the primary tumor extent and thickness
2. Lymph node dissection and removal of lymph node metastases
3. Consideration of radiochemotherapy (limited evidence as to the benefit of postoperative radiotherapy exists for other anatomical sites).

2.6.1 Surgery

Principles defined by the first tumor resection in 1857 remain viable today in that the treatment of all melanomas should be performed by wide resection. Cutaneous melanomas are still treated by that principle to avoid local recurrence (Essner, 2003, Hauschild et al., 2003, Veronesi and Cascinelli, 1979). Limited excision of the primary lesion as well as excisional and incisional biopsies are associated with an increased risk of causing accidental dissemination of malignant cells within the adjacent tissues or even into the blood or lymphatic stream with probable devastating consequences (Harter et al., 1992, Kusukawa et al., 2000).
The surgical margin also depends on the thickness of the tumor. In patients with tumors less than 1 mm thickness, a surgical margin of 1 cm has been shown to be adequate, compared with wide tumor margin resections of 3 cm (Veronesi et al., 1988). None of these patients developed local recurrence in the follow-up period revealing an adequate resection extent. In patients with tumor thickness of 1 to 2mm local recurrences were found in both study groups of patients receiving resection margins of 1 cm or 3 cm without significant differences, although more recurrences were found in the 1 cm group (Veronesi et al., 1988). The evidence, that resections of 1 to 2 cm around the tumor are sufficient and show similar results in local control and overall survival, have been also found by other studies comparing the long term results of different resection protocols in varying tumor extent and thicknesses (Balch et al., 1993, Heaton et al., 1998). The local recurrence rate in these studies is 1.7% with 2 cm surgical margin compared with 0.8% with 4 cm after six years without statistically significant differences (Balch et al., 1993, Heaton et al., 1998). The surgical therapy within the oral cavity remains problematic because wide resection margins require also reconstruction techniques after tumor ablation to avoid mutilation, functional impairment and a poor quality of life (Mücke et al., 2009, Mücke et al., 2011, Mücke et al., 2010). In some instances the suggested resection margins would compromise vital structures which mean a compromise between theoretically ideal margins and postoperative function and quality of life must be made.
Regional lymph nodes are the most common sites of metastases for all melanomas. Palpable lymph nodes in the neck or fixed to the adjacent tissues should be suspicious for metastases. Radiologically, lymph nodes larger than 1 cm must also be considered to be involved by metastases. There exists a correlation between the tumor thickness and the occurrence of regional lymph node metastases. Primary lesions less than 1 mm thickness are considered to yield a rate of < 10% lymph node metastases, 1.01 to 2.00 mm are accounting for about 20%, 2.01 to 4.00 mm are accounting for 33%, and >4.00 mm are associated with a risk of

lymph node involvement of more than 40% at the time of staging (Morton et al., 2005, Morton et al., 2003, Morton et al., 1993). Another study evaluated an exponential increasing of lymph node metastases if the tumor becomes thicker. A thickness of 0.76 to 1.50 mm was associated with regional lymph node metastases in 2 to 25% of cases. In tumors with a thickness between 1.51 to 4.00 mm the rate of regional lymph node metastases developed to 57%. A tumor thickness larger than 4 mm was associated with microscopic presence of metastases within the lymph nodes (Balch, 1999, Balch et al., 2000, Balch et al., 1996). There has been evidence that lymph node dissection resulted in an increase of overall survival compared to patients receiving palliative treatment to the neck only (Balch, 1999, Balch et al., 2000, Balch et al., 1996, Balch et al., 1993, Cascinelli et al., 1998). Negative lymph nodes are a strong prognostic factor for survival, whereas lymph node metastases yield a 6 times higher relative risk for death (Balch et al., 2009, Gershenwald et al., 1999).

Patients who suffered from oral mucosal malignant melanomas are often diagnosed at an advanced stage followed by ulceration, microsatellites or regional nodal metastases (Chaudhry et al., 1958, Morton et al., 1993, Mücke et al., 2009, Patel et al., 2002, Prasad et al., 2004, Rapidis et al., 2003, Temam et al., 2005). This high rate of regional lymph node metastases means that patients at risk should be considered for therapeutic elective neck dissection with a low threshold for surgery. Although no randomized trials on the treatment of the regional lymph nodes for oral mucosal malignant melanoma exist due to the rarity of this tumor, there is little doubt about this treatment approach. (Balch et al., 2009, Balch et al., 1996, Cascinelli et al., 1998, Chaudhry et al., 1958, Essner, 2003, Hauschild et al., 2003, Medina et al., 2003, Morton et al., 2003, Morton et al., 1993, Mücke et al., 2009, Patel et al., 2002, Tanaka et al., 2004, Temam et al., 2005). As the oral melanoma is very aggressive and the texture of the mucosa is different from the cutis with an earlier occurrence of lymph node metastases, there is actually no role for the sentinel lymph node technique, as the risk of micrometastases has to be excluded by standard therapeutic neck dissection (Prasad et al., 2004, Snow and van der Waal, 1986, Umeda and Shimada, 1994).

2.6.2 Radiotherapy

Radiotherapy has been used to control local recurrence (Balch et al., 1993, Harwood, 1983, Schmidt-Ullrich and Johnson, 1996, Storper et al., 1993). Postoperative, adjuvant radiation therapy results in a lower local recurrence rate in comparison to patients without radiotherapy treated by wide surgical resection only (Harwood, 1983). Hyperfractionated accelerated radiotherapies have appeared most useful (Harwood, 1983, Schmidt-Ullrich and Johnson, 1996, Storper et al., 1993), although the differences were not found to be statistically significant. The adjuvant performance of radiotherapy should be considered in advanced stage malignant melanomas of the oral cavity. There are still no data available from randomized trials regarding the efficacy of adjuvant radiotherapy.

2.7 Adjuvant therapy

Adjuvant therapy modalities vary and include the application of non-specific immunostimulants (Grooms et al., 1977, Morton et al., 1970, Morton et al., 1974, Sondak and Wolfe, 1997), specific immunstimulants (Interferons), vaccination therapy, cytotoxic chemotherapy, and target-therapy.

Non-specific immunstimulants like Bacille Calmette-Guérin *(*BCG), Cryptosporidium parvum, Levanisole, thymosin, isoprinosine, transfer factor and retinoids, and interleukin

had been applied by local injection into the tumor (Grooms et al., 1977, Morton et al., 1970, Morton et al., 1974, Sondak and Wolfe, 1997). Although some authors reported limited evidence that survival was increased by this therapy this adjuvant therapy failed to prove an advantage in comparison with control treatment of any kind. Most studies performed were retrospective studies (Grooms et al., 1977, Morton et al., 1970, Morton et al., 1974, Sondak and Wolfe, 1997).

After non-specific immunostimulants have failed to establish an effect on overall survival or an improvement of symptoms, attention was paid to more specific immunostimulants such as Interferons. These glycoproteins showed a immunmodulatory and anti-tumoral effect, which was thought to be beneficial in melanoma patients. Expression of major histocompatibility complex molecules, enhancing of antigen presentation by dendritic cells, inhibition of angiogenesis, and a directly antiproliferative effect combined with the expression of melanoma-specific antigen and the stimulation of natural killer cells directly affecting the tumor was a promising treatment modality (Ascierto and Kirkwood, 2008, Janku and Kurzrock, 2010, Jonasch and Haluska, 2001, Jonasch et al., 2000, Kalani et al., 2008, Pfeffer et al., 1998). Unfortunaetly early enthusiasm has waned and this strategy is more and more critically debated (Janku and Kurzrock, 2010). The effect of interferon-α (IFN-α) has been well evaluated in different clinical trials in melanoma patients and a dose-dependent and duration-dependent effect has been found, especially in high-risk patients with the presence of lymph node metastases or thick melanoma patients (Kirkwood et al., 2001, Kirkwood et al., 1996, Punt and Eggermont, 2001). In contrast, high-dose IFN-α is often associated with severe toxicity (Eggermont, 2002, Eggermont and Gore, 2002), and the outcome reported by the Southwest Oncology Group revealed no clinical benefit for patients who received adjuvant therapy. Indeed they may have done worse when compared to the patients who received no adjuvant therapy (Barth and Morton, 1995, Taylor et al., 1992).

Another adjuvant method for the therapy of melanoma patients are vaccination therapies. Based on the evidence that the immune system plays a natural role in melanoma progression in the same way that the previous treatment modalities tried to act at the same mechanism, vaccination therapy is designed to activate the host immune response to tumor - associated antigens. In the lack of information about specific tumor antigens, the tumor cell was the best source of antigens for activating the immune system (Hersey et al., 2002, Hersey et al., 1987, Sun et al., 1999). Previous methods of producing vaccines are always based on tumor cell preparations, but there is still no role for vaccination therapies in oral malignant melanomas.

The most established therapy beside surgery combined with radiotherapy remains cytotoxic chemotherapy. Multiple trials about a variety of cytotoxic drugs in adjuvant treatment have been performed but no study demonstrated benefits of adjuvant chemotherapy in melanoma patients at high risk for relapse or affecting overall survival significantly in controlled randomized trials. The mainstay of chemotherapy remains the palliative situation. The mainstays of cytotoxic chemotherapy include; dacarbazine, the nitrosoureas, the vinca alkaloids, cisplatin, paclitaxel, and bleomycin. The use of additional chemotherapeutic agents is still evolving. Single-drug therapy with dacarbazine reported an objective response in 18-22% of patients with measurable metastatic disease (Hill et al., 1979, Hill et al., 1981, Houghton et al., 2006, Houghton et al., 1996, Lee et al., 1995). Some trials describe efficacy of dacarbazine as a postsurgical adjuvant, but suggested no significant clinical benefit in the treatment of patients with high risk melanoma (Hill et al., 1979, Hill et al., 1981, Veronesi et al., 1982). Multiagent cytotoxic therapy is similarly unhelpful in the

adjuvant setting. Other trials of multiagent chemotherapy using nitrosoureas, dactinomycin and vincristine present contrary results (1983, Castel et al., 1991, McClay et al., 2000, Pawlik and Sondak, 2003, Wood et al., 1978).

3. Conclusion

The incidence of oral melanoma is very low and results of the treatment are still poor partly due to the advanced stage of tumor at presentation. No single management strategy or guideline can be considered the standard of care on the basis of current data. Within the head and neck the extent of the tumor, spread to the regional lymph nodes, systemic disease and histopathological variables have to be integrated into the disease staging and related to the patients' co-morbidities and personal aims. Radicality of resection has to be balanced against the feasibility of reconstruction of the resected area obtaining form and function as well as the quality of life the patient requires. Treatment of oral mucosal malignant melanoma may not be entirely consistent with the treatment of cutaneous malignant melanoma. The thickness of the primary lesion, stage of regional lymph nodes, sex, age, the reaction of the lesion to treatment are important factors influencing prognosis and treatment choices of the disease. To date, due to the rarity of this tumor entity, no randomized trials exist demonstrating any optimal treatment algorithm.

Multicenter studies collecting data about the treatment strategies and outcomes of patients suffering from oral malignant melanomas are necessary to identify the best treatment algorithm based on patient related clinical work. Oral melanomas are different from cutaneous melanomas and such studies would provide us a far better insight into their behaviour. The tumor thickness is a variable that most accurately determines therapy and prognoses, therefore, the extent of surgery margins should be decided based on the invasive depth of the primary lesion, the neck addressed on the basis of imaging staging but with a low threshold for intervention. Reconstruction follows conventional approaches but adjuvant therapy is currently disappointing.

An increasing understanding of tumour immunology and biology has led to innovative therapies which are necessary if an effective treatment for oral malignant melanomas is to be developed in the future. The application of new or established technologies in experimental tumor models is necessary to increase the potential for such treatments (e.g. proteomics, targeted therapy, vaccination therapy), but is currently still an area of experimentation and hope rather than pragmatic clinical practice.

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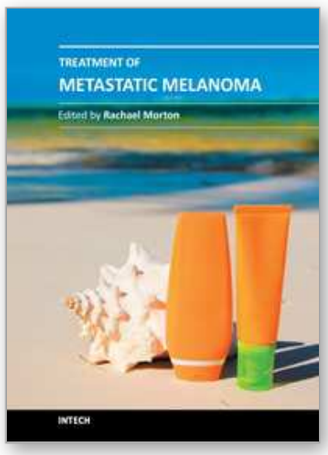

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Surgery continues to be the mainstay treatment for melanoma localized to the primary tumor and/or lymph nodes. Results from randomized controlled trials indicate that sentinel node biopsy for the treatment of cutaneous melanoma of intermediate thickness has a beneficial effect on recurrence rates, and adjuvant radiotherapy to regional lymph node fields following surgical resection reduces loco-regional recurrence in patients at high risk of relapse. Isolated limb perfusion, electrochemotherapy, and photodynamic therapy continue to be evaluated for treatment of stage IV disease. However, the greatest excitement in new treatment has been with targeted therapies for genetic mutations. In particular, the promising results of partial and complete tumor response in stage IV disease from early phase trials of the B-RAF kinase inhibitors. This book provides a contemporary insight into the therapeutic treatment options for patients with metastatic melanoma and is relevant to clinicians and researchers worldwide. In addition, an update on current clinical trials for melanoma treatment has been included, and two chapters have been reserved to discuss the treatment of oral and uveal melanoma.

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